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EXAMINER

CHERNYSHEV, OLGA N

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1649

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/066,500

Applicant(s)

ASHKENAZI ET AL.

Examiner

Olga N. Chernyshev

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 40-47, 50-52 and 56-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40-47, 50-52 and 56-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Formal matters

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Respond to amendment

2. Claims 40-47 and 50-51 have been amended, claim 53 has been canceled and claims 60-72 have been added as requested in the amendment filed on June 17, 2005. Following the amendment, claims 40-47, 50-52 and 56-72 are pending in the instant application.
3. Claims 40-47, 50-52 and 56-72 are under examination in the instant office action.
4. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
5. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.
6. Applicant's arguments filed on June 17, 2005 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

7. Claims 40-47, 50-52 and 56-72 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record as applied to claims 40-47, 50-53 and 56-59 in section 6 of Paper mailed on March 16, 2005 and also in previous office actions of record.

Applicant traverses the rejection by discussing legal standards of 35 U.S.C. 101, refers to Utility Examination Guidelines and appropriate case law related to utility requirement (pages 9-11 of the Response). Applicant's review of the issue of utility and case law that has been cited is not disputed by the Examiner. The disagreement, however, remains as to what constitutes a specific and substantial credible "real world" utility.

The claimed isolated nucleic acids are asserted to be "useful for the diagnosis and treatment of pericyte-associated tumors and for the stimulation of angiogenesis" (bottom of page 11 of the Response). The Examiner maintains the position that these three asserted utilities are not supported by any factual evidence of record or sound scientific reasoning in the instant specification, as filed. The only information presented in the instant specification regarding PRO444 polypeptide encoded by the claimed nucleic acid molecules is disclosed in the Example 60, which shows that PRO444 polypeptide of SEQ ID NO: 9 induced the expression of c-fos in pericyte cells (page 142). Because there is no disclosure that PRO444 polypeptides or polynucleotides are exclusively present/absent or expressed at the altered levels in pericyte-associated tumors, one would clearly not be able to use PRO444 nucleic acids as cancer markers, therefore, the asserted utility of PRO444 for diagnosis of pericyte-associated tumors is not specific or substantial. Second, because many factors and signals have capability of activating c-fos and because the role of c-fos transcription factor is not limited to cancer (see reasons of record and references to scientific publication presented in the previous office actions of record), there is no scientific support for conclusion that activation of c-fos in pericytes by PRO444 is specifically associated with carcinogenesis of pericytes. Thus, the claimed PRO444 nucleic acids cannot be used for treatment of pericyte-associated tumors. Third, the instant specification

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provides no evidence or reliance to scientific publications to support a nexus between activation of c-fos in pericytes and angiogenesis. The art teaches that process of angiogenesis or neovascularization is very complex and that the involvement of pericytes in angiogenesis is controversial and not fully understood (see references of record in the previous office actions and also Diaz-Florez et al., *Histol. Histopath.*, 1994, Vol. 9, pp.807-843, pages 807, 812 and 817-818 specifically). There appears to be no indication provided by Applicant or known in the art that would directly connect activation of c-fos in pericytes and angiogenesis. Therefore, Applicant's asserted utilities, particularly in view of a lack of knowledge as to the biological significance of the polypeptide of SEQ ID NO: 9 with respect to cancer or angiogenesis, the type of cancer which can be diagnosed, and how much of the nucleic acid molecule of SEQ ID NO: 8 is indicative of disease, constitutes a utility that requires further research to identify or reasonably confirm a "real world" context of use, see *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966).

Applicant submits a summary of arguments and the disputes issues involved at page 12 of the Response. Applicant's arguments are answered in order as presented on page 12 and further within the text of the Response.

Applicant submits that "The Examiner argues that there is no evidence that *c-fos* induction is associated with cancer or angiogenesis" (page 12) and refers to articles by Saez et al., Marconcini et al. and McColl et al. and states that "one skilled in the art would believe that it is more likely than not that PRO444, an inducer of *c-fos* activity in cells having a known role in angiogenesis, (*i.e.*, pericytes), is useful as an angiogenic factor". However, Applicant mischaracterizes the Examiner's position. It was never argued by the Examiner that *c-fos* induction is not associated with cancer or angiogenesis. As fully explained earlier, the art

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recognizes that *c-fos* proto-oncogene plays a role in cell differentiation and transformation and because these processes are strongly related to tumor pathology, the role of *c-fos* transcription factor in cancer has been closely investigated. Further, the Examiner presented several review articles, which clearly explain that activation of immediate-early genes, such as *c-fos*, is caused by a wide variety of stimuli. For example, Janknecht et al. teaches that *c-fos* could be activated by growth factors, serum and UV-light; Herrera et al. indicates *c-fos* induction in response to seizures (see both articles cited with Paper mailed on April 28, 2004); *c-fos* could be induced by increased intracellular calcium (Coulon et al, Paper mailed on March 16, 2005). Therefore, one skilled in the art would immediately appreciate that not every stimulus that results in activation of *c-fos* relates to its role in cancer, such role not currently fully established in the art.

Applicant's reasoning and reference to publications of Saez et al. and Marconcini et al. (page 12 continuing to page 13 of the Response) does not substantiate for the link between activation of *c-fos* by PRO444 in pericytes and cancer of pericytes. With respect to publication of McColl et al., 2004 (middle at page 13), Applicant is reminded that the utility of the claimed invention must be established and fully disclosed at the time of filing and, therefore, cannot be supported by reference to a post-filing disclosure.

At pages 13-14 of the Response, Applicant refers to *In re Oetiker* and *In re Brana* and submits that the evidentiary standard for utility is "a preponderance of the evidence", or "more likely than not" standard". Applicant further criticizes the references presented by the Examiner in the previous office actions of record stating that "the fact that other regulators of *c-fos* exist has no bearing on Applicant's asserted utilities (*e.g.*, as a diagnostic or therapeutic target for pericyte associated tumors, or as an angiogenic agent). Applicants have provided evidence that

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PRO444 stimulates *c-fos* in pericyte cells" (bottom at page 15). Applicant's arguments have been fully considered but are not persuasive for the following reasons.

It appears that Applicant has taken the position that because PRO444 activates *c-fos* expression in pericytes (with no comparison to other cell types), and because *c-fos* plays a role in cell differentiation/ transformation, than PRO444 is indicative of or could be used for treatment of pericyte-associated tumors. Also, again, because PRO444 activated *c-fos* expression in pericytes, and because pericytes are the cells present in blood vessel wall, than PRO444 is associated with angiogenesis in pericyte cells. The issue, however, remains that at the time of invention, no disclosure in the form of factual data or reliance to scientific reasoning of relevance of *c-fos* activation by PRO444 polypeptides in pericytes to diagnosis or treatment of cancer in pericytes or formation of blood vessels has not been presented. The fact that PRO444 polypeptides induced *c-fos* in pericytes does not provide for immediate use of PRO444 encoding nucleic acid molecules as markers for cancer or for treatment of cancer or for stimulation of blood vessel formation. There is little doubt that, after complete characterization of the biological role of PRO444 in *c-fos* activation, this polypeptide and encoding nucleic acid molecules may be found to have a specific role in cancer and angiogenesis, which would support their specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. While the nucleic acid molecule that encodes a polypeptide that has a stated correlation to a specific disease condition or physiological function would be considered a "substantial utility" in the context of identifying potential candidates for preventive or therapeutic measures, in the instant case the claimed nucleic acids are suitable only for additional research. The instant situation is directly

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analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court expressed the opinion that all chemical compounds are “useful” as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed “real world” utility.

To employ a nucleic acid of the instant invention in methods of diagnosis or treatment of cancer conditions or for angiogenesis, as currently asserted, would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible “real world” use for the encoded protein in their currently available form, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

8. Claims 40-47, 50-52 and 56-72 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.
9. Claims 40-44, as amended, and claims 56-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for those reasons of record in section 8 of Paper mailed on March 16, 2005 and reason in previous office actions of record.

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Applicant is advised that because claims 56-59 are dependent from claim 40, which was originally rejected under 35 U.S.C. 112, first paragraph, lack of written description, claims 56-59 should have been properly rejected as being dependent from the claim that lacks written description. Because the dependency of claims 56-59 has been overlooked by the Examiner during examination of the instant case, the claims were not included within the text of the rejection in previous office actions of record. There is no new grounds of rejection added to claims 56-59 in the instant office action, as the claims include limitations of the previously rejected claim 40.

At pages 18-20 of the Response, Applicant discusses the legal standards for written description requirement and argues the compliance of claims wherein the recitation of hybridization condition is present. Because the instant claims 40-44 and 56-59 do not contain recitations of hybridization conditions, Applicant's arguments with respect to this matter are considered to be moot.

At bottom of page 20, Applicant submits that the claims containing recitation of percent identity to the amino acid sequence of SEQ ID NO: 9 "with the functional recitation "wherein said isolated nucleic acid encodes a polypeptide having the ability to induce c-fos expression" are also adequately described and refers to Example 14 of the written description training material. Applicant's arguments have been fully considered but are not persuasive for the reasons that follow.

The instant claims are directed to the genus of nucleic acids that are structurally related to the only molecule that is fully disclosed in the instant specification, the nucleic acid encoding a polypeptide of SEQ ID NO: 9, wherein the polypeptide has the ability to induce c-fos expression.

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As fully explained in the previous office actions of record, the instant specification fails to provide sufficient written description of the claimed molecules in such form that a person skilled in the art could immediately envision the complete chemical structure of claimed invention and reasonably conclude that the Inventor was in possession of the claimed invention. Whereas one can readily produce any polynucleotide, which is at least 80% identical to SEQ ID NO: 8, one would have no idea, which of those polynucleotides would encode a polypeptide having the ability to induce c-fos expression.

Furthermore, in Example 14 of the written description training material, the claims were directed to a genus of proteins having 95% identity to the protein of the disclosed sequence (SEQ ID NO: 3) and capable to catalyze the specific reaction. The procedures of making proteins with 95% identity and also assay, which will identify proteins with the recited catalytic activity, were known and disclosed. In the instant case, what is essential to the operation of the instant invention is a nucleic acid molecule that encodes a protein with a limited defined structural similarity to the SEQ ID NO: 9 and having the ability to induce c-fos. As explained earlier, a person of skill in the art can easily envision the genus of nucleic acid molecules encoding a polypeptide, which is 80%, 85%, 90%, 95% or 99% identical to the polypeptide of SEQ ID NO: 9; however, the instant specification fails to provide a written description of those nucleic acids within this genus that are coupled with the recited function. There is no information presented regarding a distinguished structural feature that must be conserved and is common for all the molecules within the genus, or representative number of species, method of production or any other characteristic that would allow a skilled artisan to immediately understand what is claimed. Moreover, because the instant specification fails to disclose the biological function specifically

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attributed to the claimed PRO444 molecules (see reasons of record in section 7 above and also earlier office actions in sections related to utility rejection), and because according to the state of the art c-fos activation represents a non-specific cellular response to a variety of stimuli, the presence of “functional” limitation in the claims (“having ability to induce c-fos expression”) does not allow a person skilled in relevant art unequivocally distinguish those members of the claimed genus that have limited structural similarity to SEQ ID NO: 8 and have the ability to induce c-fos from the molecules that only have the structural similarity to SEQ ID NO: 8.

With respect to Applicant’s arguments regarding other US Patents (page 21 of the Response), it is well settled that the prosecution of one patent application does not affect the prosecution of an unrelated application. *In re Wertheim*, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976) (holding that “[I]t is immaterial in *ex parte* prosecution whether the same or similar claims have been allowed to others”). Accordingly, Applicant’s arguments are unavailing.

Therefore, for reasons set forth above, Applicant’s arguments have been fully and carefully considered, but are not considered persuasive and the instant rejection is maintained.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**


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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

July 19, 2005